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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,483	WU ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 1/12/05. Applicant has canceled claims 1 and 2. Claims 3-11 are new. There are nine claims pending and nine under consideration. Claims 3-11 are method of making claims. This is the second action on the merits. The application concerns some syntheses of quinazoline compounds.

Election/Restrictions

2. Applicant's election without traverse of Group I in the reply filed on 1/12/05 is acknowledged.

Response to Amendment

3. Applicants new claims, title, and abstract overcome the objections made in points #6-#8 of the previous office action. Applicants' new formula Ib, with all double bonds intact, overcomes the indefiniteness rejection made in point #9 of that action. Applicants' new formula also overcomes the indefiniteness rejection made in point #12. Applicants rewriting of the claims to put the first four steps of the reaction sequence into Jepson form overcomes the indefiniteness rejections made in points #13-#17. Applicants' new claims, which require a Horner-type reaction, are patentable over Nair ('251) as discussed in point #20 of the previous office action. Nair ('251) employs an aldol-type coupling process, not the Wittig or Horner process presently required. In view of the abandonment of application 10/627,485 on 2/11/05, the double patenting rejection made in point #21 is moot.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 4, claim 3 "or a nitrogen or oxygen protecting group" is indefinite. There are three issues. Firstly, this phrase is not defined in the specification. What is the structure of this claimed protecting group? Secondly, from what is the nitrogen or oxygen to be protected? Are these protecting groups acid stable but removed by base like an acetate group on oxygen? Are these protecting groups base stable but removed by acid like a t-BOC group on nitrogen? Thirdly, are these protecting groups attached through nitrogen and oxygen or directly attached to the pyrimidine ring? A literal reading of the claim is that R_1 and R_2 = -C(O)-OBu^t or $-CH_2C_6H_5$ when the protecting group is BOC or Bzl. Is this intended? The Examiner suggests deleting the phrase.

Applicants make four arguments concerning this rejection. They argue that the artisan using the invention would be a graduate chemist. They cite Greene's book on protecting groups as evidence that the term "protecting group" is well

known in the chemical arts. They state that the protecting groups are to protect the molecules against base. And finally, they state that the protecting groups are not attached directly to the quinazoline ring as radicals R_1 and R_2 but rather are connected through oxygen or nitrogen atoms. That is not persuasive.

Firstly, the chemist making Applicants compounds for their intended medical use would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. He would know the concept of protecting group but be unaware of which specific protecting groups Applicants are attempting to embrace. He would be a graduate chemist since he had graduated from college but typically Ph.D. chemists do not work in the large-scale facilities used to prepare clinical quantities of compounds.

Secondly, nowhere does the specification refer to the Greene text. In any case, since the structure of the claimed protecting groups is essential to establish the metes and bounds of the claims, the incorporation by reference of essential material in the specification by reference to a publication is improper. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Thirdly, while Applicants statement that their protecting groups are to protect against base, no such limitation occurs in either the specification or the claims. When functional terms like "protecting group" are used in claims, there must be some method apparent to determine how much protection is required and against what. The present specification contains no such data. Fourthly, while Applicants intention to attached their nitrogen and oxygen protecting groups to the quinazoline through a nitrogen or oxygen atom, which is not what the claim literally says. The protecting group BOC, which can protect either the oxygen of an alcohol or a nitrogen atom of an amine, has the structure -C(O)-OBu^t. Protecting an alcohol or an amine, the group would have the partial structure O-C(O)-OBu^t or NH-C(O)-OBu^t. However, Applicants' claim literally states that the protecting group itself is either radical R_1 or radical R_2. Thus, now the claim states that R_1 or R_2 includes -C(O)-OBu^t, not O-C(O)-OBu^t or NH-C(O)-OBu^t, which is not Applicants stated intention. See MPEP §2172 II.

5. Claims 3-5 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 7, claim 3, "an amino acid residue" is indefinite. This is not defined in the specification but in the passage spanning line 19, page 6 to line 2, page 7, glutamic acid and aspartic acid

are offered as examples. Is this all? Are the twenty natural amino acids that are coded by DNA intended? Are all carboxylic acids with an amino group in the α-position intended? Could this phrase include all organic acid residues containing an amino group somewhere in the molecule, including the acids of sulfur, phosphorus, and boron? How is the residue attached to C(O)-? Must it be through the amino group or can it be attached anywhere?

Applicants make three arguments concerning this rejection. They point to the paragraph spanning pages 6 to 7, of the specification, they state that the twenty natural amino acids are intended, and finally they state that all radicals containing both an amino group and any kind of acid group are intended. This is not persuasive because now of these arguments allow the skilled chemist to draw all the radicals, which Applicants intend to claim. The passage on page 7 says "other amino acids may be employed". fine, what are their structures. The argument that the twenty natural α-amino acids are intended would appear to be at odds with the final argument that radicals derived from such amino acids such as 6-aminohexylphosphonic acid are also intended.

6. Claims 3-8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: the reduction

reaction required to convert the olefin product of the reaction of the formyl quinazoline with the phosphonate compound to the saturated compound Ib. The product of the process claimed in claim 3 is not the saturated compound Ib but is rather the olefin pictured at the bottom of page 10. The necessity of the reduction step is discussed in the paragraph spanning pages 11 to 12. The present formula Ib corresponds to the product of Example 7. The compound produced by the procedure outlines in the last four lines of claim 3 corresponds to the product of Example 6.

7. Claims 3, 4, and 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 13, claim 3, "benzoic acid alkylene moiety" is too functional. The phrase does not have an established conventional meaning in organic chemistry that identifies staring materials short of every atom or functional group capable of being further transformed into the benzoic acid phosphonate intermediate. What radicals do Applicants intended here? In Example 5, page 16 the "alkylene moiety" is a bromomethyl group. Is this all that is intended? Could it be a methyl group alone? How about a benzyl alcohol? The Examiner suggests using Example 5, page 16 to clarify what is meant here.

8. Claims 3-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The chemical name in line 14, claim 3, "alkyldiethylphosphite" is improper. The intermediate that Applicants use is a phosphonate compound. A phosphite has three single bonds from phosphorus to oxygen and none to carbon. A phosphonate has two single bonds from phosphorus to oxygen, one double bond to oxygen, and one bond to carbon. Applicants have correctly named their intermediate in line 17, page 17 of the specification.

9. Claims 3, 4, and 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for performing the Horner reaction with X = alkoxy or an amino acid residue, does not reasonably provide enablement for performing the Horner reaction with X = hydroxy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The to use rejection, when applied to a process claim refers to the operability of the process. When X = hydroxy, the phosphonate intermediate is a free carboxylic acid. Deprotonation of this phosphonate compound with the sodium methoxide used by Applicants will remove a proton from the carboxyl group and not the phosphonate methylene group.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-5, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan (J. Heterocyclic Chem.) in view of House (Modern Synthetic Reactions, Second edition). . The reference teaches a synthetic process to make a compound of formula Ib with $R_1 = R_2$ = amino, R_3 = hydrogen, X_1-X_4 = carbon, R_4 = C(O)-X, and X = L-glutamic acid diethyl ester. The process taught in the reference uses a Wittig reaction employing an ylide derived from triphenylphosphine. The Applicant claims such a process using a Horner reaction using a phosphonate derived from triethyl phosphite. The process is shown in the reference in is taught in columns 2, page 542 and column 1, page 543. The reaction sequence is pictured in the reference in the scheme at the bottom of page 541, the second paragraph page 542, and the second scheme on page 542. The synthesis of the formyl quinazoline from the benzonitrile is found in the scheme at the bottom of page 541, second column. The difference between the claimed and taught processes is the phosphorus reagent used to react with the benzoic acid moiety to form the coupling

reagent. The prior art teaches triphenylphosphine and Applicants claims triethyl phosphite.

The interchangeability of the two phosphorus reagents and the motivation to substitute triethyl phosphite are found in House (Modern Synthetic Reactions, Second edition). In the first complete paragraph on page 690, House (Modern Synthetic Reactions, Second edition) states that phosphonate compounds, which are derived from triethyl phosphite, are "a modification of the Wittig reaction *** which has proved of value". The intermediate of Applicants Example 5 is a phosphonate compound as discussed above in the indefiniteness rejection. The motivation to replace the triphenylphosphine by triethyl phosphite is found in the last sentence in page 690 of the secondary reference. The triphenylphosphine oxide by-product produced in the reaction taught by Yan (J. Heterocyclic Chem.) is both bulky and very difficult to separate from the olefin products. The phosphate salt produced by Applicants claimed procedure is easily removed from the product by a simple extraction.

11. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan (J. Heterocyclic Chem.) in view of House (Modern Synthetic Reactions, Second edition) as applied to claims 3-5, 7, and 8 above, and further in view of *Cohn et al v. Comr. Pats* 148 USPQ 486, *Ex parte Rubin* 128 USPQ 440, *Ex parte*

Baril 124 USPQ 509, and *Ex parte Schwenk* 73 USPQ 85. Applicants' claims 9-11 require attaching glutamic acid to the benzoic acid side chain after the coupling reaction and saponification of a methyl ester to form a free benzoic acid. Yan (J. Heterocyclic Chem.) teaches attaching the glutamic acid to the benzoic acid before the coupling reaction. Merely reversing the order of steps of a multi-step process does not impart patentability to the claimed process in the absence of unexpected results.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

14. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

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TCMcK/me